REMARKS

Reconsideration and withdrawal of the claim rejections are requested in view of the amendments and remarks herein.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 21-40 are pending in this application. Claims21-39 have been amended and claim 40 has been added.

Support for the amendments can be found throughout the specification. Specifically, support for the recitation "rabies G protein or a mutant, variant, derivative or fragment thereof" in claim 21 can be found, for example, on page 12, line 16 of the specification. MLV, HIV and EIAV, as recited in claim 21, are listed as a preferred embodiment on page 13, line 29. A comparison between transduction of neuronal cells (i.e. "target site") with the retroviral vector delivery system of the invention, i.e. pseudotyping with rabies G with transduction of neuronal cells with a vector pseudotyped with a VSV-G protein, as set forth in claims 21 and 32-40, is demonstrated in Example 6 (see Table 4). A "target site" is defined on page 14, line 4, of the specification. All other amendments are made for clarity and to place the claims in better form.

No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH ARE OVERCOME

Claim 31 was rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed.

The Office Action maintains that the use for the pharmaceutical composition of claim 31 is gene therapy, and that this use is not enabled by the specification due to the unpredictability of the art. The attached Declaration under 37 C.F.R. 1.132, by Drs. Wong and Mazarakis, demonstrates that the claimed retroviral vector delivery system can be effectively employed in a

therapeutic context. The data presented in the Declaration show protection of neuronal cells from degeneration and cellular loss in a rat stroke model.

As stated in MPEP 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." (In this instance the data is presented via Declaration, rather than Example, but the effect is the same.) An animal model is acceptable where it is recognized in the art that this model correlates to a specific condition. If this is has not yet been established in the art, the animal model is acceptable if one skilled in the art would accept the model as reasonably correlating to the condition.

In the present invention, the "condition" is one which affects neuronal cells, e.g. stroke. The condition can be corrected by the introduction of the nucleic acid encoding the anti-apoptotic Bcl2 protein into the subject, so that the genetic phenotype of the subject is altered. When testing a suitable vector for delivery of the gene product, a good experimental model should test whether 1) the gene product is successfully introduced into a cell and whether 2) the genetic phenotype of the cell is altered as a result. In this case, the cells in question have clearly passed this test, as neuronal protection is demonstrated in the experimental model.

This "reasonableness" standard serves to prevent the PTO from unnecessarily and inappropriately adopting the more stringent standards of the FDA. [1]

As demonstrated by the examples and by the Declaration of Drs. Wong and Mazarakis, administration of an exogenous gene using the claimed vector system is feasible, as is evidenced by the results presented.

It is respectfully submitted that adequate guidance is provided to enable the skilled artisan to practice the claimed invention without undue experimentation. Therefore, reconsideration and withdrawal of the U.S.C. § 112, first paragraph rejections are earnestly solicited.

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[1] Public hearings were held in San Diego on October 17, 1994, where then PTO Commissioner Bruce Lehman and other PTO representatives received comments on the inappropriate standards that Examiners were applying to biotechnological inventions and as a result of these and other objections raised by the scientific community, the present "reasonableness" standard is now applied.

III. THE ART REJECTIONS ARE OVERCOME

Claims 21-24, 26-30 and 34-39 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Bremel *et al.* Claim 25 was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bremel *et al.* in view of Olsen *et al.* Claims 32-33 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bremel *et al.* These rejections are traversed and will be addressed collectively.

The Office Action asserts that the neuronal transduction capability of a rabies whole virus, which is regulated by the rabies G glycoprotein, is an inherent property. The Office Action relies on Gaudin *et al.* & Morimoto *et al.* to set forth the knowledge available to the skilled artisan. As such, the Office Action asserts, on page 4, that "the retrovirus pseudotyped with rabies G glycoprotein (as disclosed by Bremel *et al.*) would inherently possess a greater tropism for neuronal cells than a retrovirus without rabies virus G glycoprotein." Page 5 of the Office Action also asserts that Bremel *et al.* describe rabies G pseudotyped retroviral vectors, pointing to columns 6-10.

This position is improper under 102(e) and 103.

Bremel *et al.* relates to the use of retroviral vectors for the generation of transgenic non-human animals. The retroviral vectors of Bremel *et al.* provide for an improved efficiency in the generation of animals carrying the transgene in the germ cells. See col. 24, lines 5-10. Bremel *et al.* specifically state that retroviral vectors providing this improvement are pseudotyped with the VSV-G protein because their technology required an extremely broad host range, as was indicative of VSV. See col. 9, lines 44-61. Bremel *et al.* point to the fact that VSV-G is distinguished from other retroviral envelope proteins that bind to specific cell surface receptors to gain entry into a cell. Bremel *et al.* go on to state that VSV-G is independent of the presence of specific receptors, and rather, interacts with a phospholipid component of the plasma membrane. See col. 9, lines 44-61. Bremel *et al.* support the disclosed 'improvement' in the transgenic field only with respect to the use of VSV-G pseudotyped retroviral vectors. See Experimental Section. As such, Bremel *et al.* fail to provide an enabling disclosure for the generation of rabies G pseudotyped retroviral vectors.

Bremel *et al.* is, at most "obvious-to-try", which is not the standard for determining obviousness under 103. *In re Fine*, 5USPQ 1596 (Fed. Cir. 1988).

While it is conceded that Bremel *et al.* provide a list of known G proteins which may be applicable for pseudotyping a retroviral vector, they fail to teach how to produce such pseudotyped vectors (other than a VSV-G pseudotyped retroviral vector) with a reasonable expectation of success, and further fail to teach how to use such pseudotyped vectors (other than a VSV-G pseudotype) for improving transgene efficiency. Rather, Bremel *et al.* seem to teach away from the use of other G proteins, since the VSV-G protein has a natural ability to target an 'extremely broad host range', and such tropism appears necessary for achieving the disclosed 'improvement' in transgene efficiency. See col. 9, lines 44-61. It is further noted that Bremel *et al.* fail to teach that the pseudotyping technology was as easy as substituting one G protein for another native retroviral envelope, as they fail to produce any other G protein retroviral pseudotypes.

The state of the art and the knowledge available to the ordinary artisan at the time the instant application was filed do not make up for the deficiencies of Bremel *et al.* The ordinary artisan would not have been able to produce a rabies G pseudotyped retroviral vector with a reasonable expectation of success given the teachings of Bremel *et al.* and the knowledge available at the time the claimed invention was made. Contrary to the assertions in the Office Action, it was not sufficient to base success on the natural tropism of the whole rabies virus. This rationale is improperly presuming one would have been able to generate a functional rabies G retroviral pseudotype with superior neuronal transduction efficiency over that of the art-recognized standard, *i.e.*, VSV-G retroviral pseudotypes. In particular, there were no clear rules for success in the field of pseudotyping. Rather, the technology clearly seemed to be unpredictable and entirely dependent upon the candidate G protein and the candidate retrovirus to be pseudotyped.

There have been numerous attempts to use the envelope or G protein from one virus for pseudotyping of another different virus. However, the process is highly variable and appears to be strongly influenced by interactions between the cytoplasmic tail of the envelope and the core proteins of the viral particle. The process by which envelope proteins are recruited into budding virions is a selective one, albeit, quite poorly understood. For example, Certo *et al.* (J. Virol. July, 1998; 72(7):5408-5413; copy attached) reported that the MLV envelope protein was not capable of pseudotyping SNV (spleen necrosis virus) even though the SNV envelope protein was known to successfully pseudotype MLV. Mammano *et al.* (J. Virol. Apr., 1997; 71(4):3341-

3345; copy attached) reported that the HIV envelope protein was not capable of pseudotyping Mu-MLV unless the cytoplasmic tail of gp41 was truncated. Mammano *et al.* also reported the surprising finding by Dorfman *et al.* (J. Virol. 1994; 68:1689-1696) that the HIV-1 envelope was not capable of pseudotyping its close lentiviral relative, visna virus, unless the visna virus N-terminal matrix domain was replaced with the matrix domain of the HIV-1 virus. In addition, Christodoulopoulos *et al.* (J. Virol. 2001; May, 2001; 75(9):4129-4138; copy attached) reported that the GaLV envelope protein was not able to form functional pseudotypes, supporting the fact that proper envelope function involves both interactions within the cytoplasmic tail and more long-range interactions between the cytoplasmic tail, the membrane-spanning region, and the ectodomain of the protein. As such, the state of the art supports Applicants assertion that there was no expectation of success that one G protein would successfully pseudotype another different virus, even when there seemed to be a level of compatibility between the viruses.

In addition, the method of generating VSV-G pseudotyped retroviral vectors is not extendable to a method for generating rabies-G pseudotyped retroviral vectors with a reasonable expectation of generating a rabies-G pseudotyped retroviral vector having a higher transduction efficiency in neuronal cells than a VSV-G pseudotyped retroviral vector. Nothing in Bremel *et al.*, when taken alone or when combined with Olsen and/or any other knowledge available to the ordinary artisan at the time the claimed invention was made, would provide the artisan with sufficient information to generate the rabies-G pseudotyped retroviral vector possessing the claimed superior transduction efficiency in neuronal cells. In particular, the VSV G and rabies G proteins share only 20% homology at the protein level (Wunner *et al.* J. Virol. 1984, 50: 691-697), while in the context of the teachings of Bremel *et al.*, preferred G proteins from Rhabodoviridae share at least 25% identity with VSV-G.

Furthermore, the claimed invention has a surprising feature when considered in light of the state of the art at the time of the invention with respect to neuronal transduction capability of VSV-G pseudotyped retroviral vectors. For instance, it was well known that VSV-G pseudotypes efficiently transduce neuronal cells. Thus, the skilled artisan would not have expected that a rabies-G pseudotype, if one could be generated successfully, would possess a higher transduction efficiency in neuronal cells than a VSV-G pseudotype. One would similarly not expect to achieve equivalent or higher titers than a VSV-G pseudotype. Even after the date of the invention, the state of the art supported that VSV-G pseudotypes were superior with

respect to titers. See Mochizuki *et al.* (J. Virol. Nov., 1998; 72(11):8873-8883; copy attached), who reported superior titers of VSV-G pseudotypes (Figure 4, page 8877).

As such, the disclosure of Bremel *et al.* is at best an "obvious-to-try" situation. It does not provide a disclosure with sufficient teaching regarding how to obtain the desired result, nor does it provide particular directions for achieving the desired result. An "obvious-to-try" situation exists when a general disclosure in the prior art may pique a scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the result achieved would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 14 USPQ2d 1741 (Fed. Cir. 1990).

Therefore, it is submitted that the claimed subject matter is novel and non-obvious over Bremel *et al.* either alone, or in combination. As such, reconsideration and withdrawal of the rejections under 35 U.S.C. §§102 and 103 are requested.

CONCLUSION

In view of the amendments, remarks, attachments and Declaration submitted herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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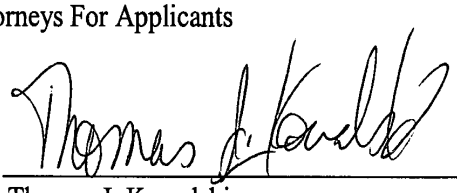
By: 

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